REMARKS

Applicant requests reconsideration of the present application in view of the foregoing amendments and the discussion that follows. The status of the claims is as follows. Claims 1-34 are pending. The Examiner has withdrawn claims 1-18 from consideration. Of the remaining claims, Claim 19 has been amended herein.

Restriction Requirement

Applicant acknowledges that the Examiner has made the original restriction requirement final and that, in making the restriction requirement, the Examiner has at least implicitly found that the delineated inventions of the original restriction requirement are, in fact, patentably distinct and patentable over each other.

The Amendment

Claim 19 was amended to delete the word "simultaneously" and to add appropriate numbering to clarify that the first reagent comprises (i) a first label, (ii) a small molecule and (iii) a drug analog, and that the second reagent comprises (i) a second label and (ii) an antibody for the small molecule. Claim 19 was also amended to refer to the predetermined increased amount of signal in step (d). Support for all of the above amendments is in the Specification, for example, original Claim 19. Claim 19 was also amended to recite that a drug analog competes with a corresponding drug, if present, for binding to antibody for the drug. Support therefor is in the Specification, for example, page 8, lines 26-29. Claim 19 was also amended to recite that the antibody for the drug binds to the drug analog of the first reagent thereby inhibiting the binding of the antibody for the small molecule to the small molecule. Support therefor is in the Specification, for example, page 27, lines 9-23.

Rejection under 35 U.S.C. §112

Claims 19-34 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicant submits that all of the specific rejections under the above code section have been obviated by the above amendments.

Rejection under 35 U.S.C. §103

Claims 19-20 and 23-26 were rejected under 35 U.S.C. 103(a) as being unpatentable over Erb, *et al.* (U.S. Patent No. 6,251,688) (Erb 1) and Erb, *et al.* (U.S. Patent No. 6,300,082) (Erb 2) in view of Zhang, *et al.*, (The Journal of Biological Chemistry, 268 (14), May15, 1993, pages 10095-10101) (Zhang).

The disclosures of Erb 1 and Erb 2 are similar. Essentially, the references disclose method and apparatus for measuring binding between a plurality of molecules of a first type such as a biological receptor and a plurality of molecules of a second type such as a type that binds to a biological receptor. The apparatus uses a sensor possessing a waveguide to which have been attached in close proximity to its surface, features resembling molecules of the first type. Light is injected into the waveguide so as to produce an evanescent field at its surface. Molecules of the second type are tagged with a tag belonging to the class of chemicals that alters a characteristic of light when light passes through the chemical tag. The tags may be chemically attached or they may be chemically attached to a molecule such as an antibody that has affinity for the molecule of interest (column 15, lines 14-34).

Erb 1 and Erb 2 do not disclose or suggest the presently claimed methods. Neither Erb 1 nor Erb 2 discloses or suggests the reagents employed in the present method. As set forth in Claim 19, the present methods use (a) an antibody for each drug suspected of being present, (b) for each of such drugs, a first reagent comprising (i) a first label, (ii) a small molecule and (iii) a drug analog, and (c) a second reagent comprising (i) a second label and (ii) an antibody for the small molecule.

In the method of the invention, the analyte drug binds to a respective antibody for the drug, which in the absence of analyte inhibits binding of the first reagent with the second reagent by binding to the drug analog of the first reagent thereby inhibiting the binding of the small molecule with antibody for the small molecule of the second reagent. Thus, in the absence of analyte drug, signal is reduced. Sample to be screened for the presence of one or more analyte drugs is combined in a suitable medium with antibodies for each of the drugs suspected of being in the sample. If one or more of the analyte drugs are present, their respective antibodies bind to them. For analytes that are absent, the antibodies for those respective analytes remain unbound.

↓ bind drug analog ?

For first reagents, the drug analogs are allowed to react with their respective unbound antibodies. For the second reagent, if an analyte drug is present, the corresponding antibody for the drug becomes bound thereto and signal is emitted because the labels of the first and second reagents come into close proximity. On the other hand, if an analyte drug is absent, the corresponding antibodies bind with the drug analogs of the first reagent and no signal production occurs relating to that analyte drug. Accordingly, an increase in signal is observed if one or more analyte drugs are present. The amount of signal is measured and related to the amount of signal corresponding to that obtained for predetermined cut-off levels for the respective analyte drugs, thus resulting in a simultaneous determination for the presence of one or more the suspected analyte drugs. The method gives a yes or no answer. If one or more of the analyte drugs is present above the predetermined cut-off levels, a yes answer is obtained. A positive or increase in signal corresponds to a yes answer.

Erb 1 and Erb 2 are deficient in not disclosing anything relevant to the aforementioned invention of Claim 19.

The Examiner recognizes at least that the references are deficient in not teaching the simultaneous detection of a plurality of drugs. However, asserts the Examiner, Zhang teaches methods of measuring the simultaneous incorporation of two anticancer drugs into DNA. It would have been obvious to one of ordinary skill in the art at the time of the invention, argues the Examiner, to employ multiple drugs as taught by Zhang in the drug detection method of Erb 1 and Erb 2 because Zhang teaches that DNA is modified by drugs in three ways (intercalation, covalent bound formation, and nucleoside analogue incorporation), and these drug modifications can co-exist in the same DNA molecule without difficulty. When drug modification exhibited by different drugs occurs in close proximity in DNA, argues the Examiner, it may provide an additive inhibitory effect for the target enzyme, in other words, increase the drug effectiveness. In other words, continues the Examiner, multiple drugs may interact symbiotically in patient systems, therein the evaluation of more than one drug simultaneously would provide information to such an effect. The Examiner concludes that one of ordinary skill in the art would have been motivated to evaluate multiple drugs in order to extrapolate various data sets for evaluation of drug synergism.

Applicant submits that, in order for one to modify the deficient teachings of the reference to achieve the methods of the present invention, one would have to use Applicant's disclosure because the references do not teach anything relevant to the multiple drug determination assay as claimed. As has been held, there must be some suggestion, motivation or teaching in the prior art whereby the person of ordinary skill would have selected the components that the inventor selected and used to make the new invention (*C.R. Bard, Inc. v M3 Systems, Inc.*, 157 F.3d 1340, 48 U.S.P.Q.2d 1225 (Fed. Cir. 1998), *cert. denied*, 67 U.S.L.W. 3715 (1999)). The Examiner alleges that Zhang provides the motivation for modifying the teachings of the references in the fanciful manner in which the Examiner has done. Applicant submits that this motivation is not sufficient to suggest the present invention to one of ordinary skill in the art. To assert that this teaching provides the motivation for combining the teaching of the references in the manner in which the Examiner has done to create the presently claimed invention goes far beyond the actual teaching of the Zhang, Erb 1 and Erb 2 references.

As indicated above, the Examiner asserts that one of ordinary skill in the art would have been motivated to evaluate multiple drugs in order to extrapolate various data sets for evaluation of drug synergism. At most, the motivation would be to evaluate multiple drugs for their incorporation into DNA. Applicant submits that there is no motivation to combine the teachings of Zhang with that of Erb 1 and Erb 2.

Applicant further submits that, even if the fanciful combination of the teachings of the references were made, one still would not be in possession of the presently claimed invention. As explained above, none of the references discloses or suggests the reagents employed by Applicant in the present methods. None of the references discloses of suggests, either individually or in combination, a simultaneous determination of the presence of one or more drugs suspected of being present in a sample using the reagents as set forth in the claims.

In addition, the Examiner appears to be using Applicant's disclosure in support of the rejection. "It is impermissible to use the claimed invention as an instruction manual or 'template' to piece together the teachings of the prior art so that the claimed invention is rendered obvious. This court has previously stated that'[o]ne cannot use hindsight

reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention." *In re Fritch*, 972 F.2d 1260, 23 USPQ 2d 1780, 1784 (Fed. Cir. 1992) (quoting *In re Fine*, 837 F.2d 1071, 1075, 5 USPQ 2d 1596, 1600 (Fed. Cir. 1988).

Claims 21 and 22 were rejected under 35 U.S.C. 103(a) as being unpatentable over Erb 1 and Erb 2 in view of Zhang and further in view of Maggio (Immunoenzyme technique I, CRC press © 1980, pages 186-187). Maggio teaches separation steps with special reference to solid phases including beads. The Examiner recognizes that Erb 1, Erb 2 and Zhang are deficient in not specifically teaching the detection assay employing a solid phase such as particles. However, argues the Examiner, Maggio discloses enzyme immunoassays wherein either the antigen or antibody is immobilized onto a solid phase. The solid phase can be particles, cellulose, polyacrylamide, agarose, discs, tubes, beads, or micro plates (microtiter plates).

For the reasons set forth above with respect to the rejections over Erb 1 and Erb 2 in view of Zhang, none of the references, either individually or incombination, discloses or suggests the methods and reagents of the present claims. Maggio does not cure these deficiencies.

Claims 27-34 were rejected under 35 U.S.C. 103(a) as being unpatentable over Erb 1 and Erb 2 in view of Zhang and in further view of Zuk, *et al.* (U.S.Patent No. 4,281,061) (Zuk). The Examiner recognizes that Erb 1, Erb 2 and Zhang fail to teach the assay as a kit. However, asserts the Examiner, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of applicant's invention to take the detection assay as taught by Erb 1 and Erb 2 in view of Zhang and format them into a kit because Zuk teaches that it is convenient to do so and one can enhance sensitivity of a method by providing reagents as a kit.

For the reasons set forth above with respect to the rejections over Erb 1 and Erb 2 in view of Zhang, none of the references either individually or incombination discloses or suggests the methods and reagents of the present claims. Zuk does not cure these deficiencies.

Prior Art Made of Record

Applicant acknowledges the Examiner's at least implicit determination that neither Lehnen (U.S. Patent No. 5,567,627) nor Terstappen, *et al.* (U.S. Patent No. 5,646,001) discloses or suggests the present invention either individually or in combination with each other or one or more of Erb 1, Erb 2, Zhang, Maggio or Zuk.

Conclusion

Claims 19-34 satisfy the requirements of 35 U.S.C. §§112 and 103. The Specification has been amended to address issues raised by the Examiner. Allowance of the above-identified patent application, it is respectfully submitted, is in order.

Respectfully submitted,

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